# Intramolecular Diastereospecific Aryl Radical Substitution

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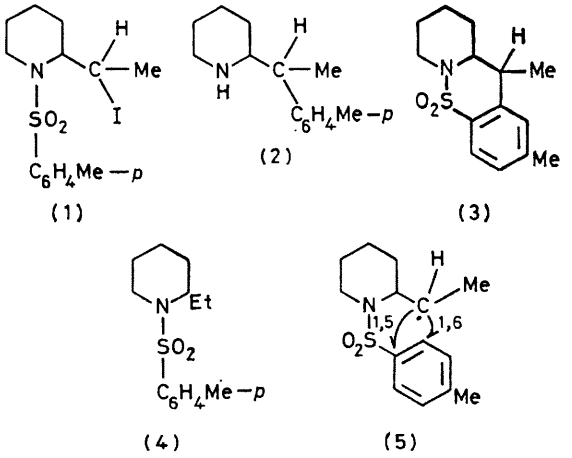
*Summary* Intramolecular aryl radical rearrangement of the chiral *N*-tosylpiperidines (**1**) proceeds along a unique stereochemical pathway depending on the geometry of the starting material.

CONTRARY to the wealth of information on the stereochemical patterns for ionic substitution reactions radical processes for substitutions have been little investigated. Undoubtedly the commonly observed racemisation at the reacting radical site has not encouraged systematic studies; therefore we present our results on the stereochemistry of the radical rearrangement of the four diastereomeric 2-(1-iodoethyl)-1-tosylpiperidines (**1**).

As reported earlier[1] the title compound (**1**) exhibits an unusual type of behaviour upon treatment with $Bu^n_3SnH$ leading to the α-benzylpiperidine (**2**) and the thiazine *SS*-dioxide (**3**). In addition, the reduced compound (**4**) is formed to a certain extent. The relative amounts of (**2**), (**3**), and (**4**) depend *inter alia* on the nature of the aryl function and the reaction temperature.

The formation of the products (**2**) and (**3**) is explained on the basis of an intramolecular 1,5- or 1,6-aryl insertion process of the assumed radical intermediate (**5**). The reaction of a chiral derivative of (**1**) would be of particular relevance in understanding the stereochemical nature of the 1,6-aryl substitutions especially with reference to the degree of racemisation at the reacting radical centre.



TABLE[a,b,d]

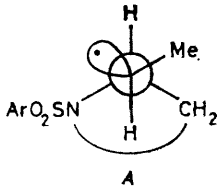
| (1) | (2) | (3) | (4) |
|---|---|---|---|
| (2*R*), (1′*S*) | (2*R*), (1′*S*)[e,f] 35%[c] m.p. HCl salt 240 °C (decomp.) | (2*R*), (1′*S*)[e,g] 18%[c] m.p. 101—103 °C | 43%[c] m.p. 38—40 °C |
| (2*R*), (1′*R*) | (2*R*), (1′*S*)[e] 35%[c] | (2*R*), (1′*S*)[e] 16%[c] | 46%[c] |
| (2*S*), (1′*S*) | (2*S*), (1′*R*)[e] [h] | (2*S*), (1′*R*)[e] [h] | [h] |
| (2*S*), (1′*R*) | (2*S*), (1′*R*)[e] [h] | (2*S*), (1′*R*)[e] [h] | [h] |

[a] Standard conditions 0·25 mmol of (**1**), 0·67 mmol of $Bu^n_3SnH$, 11 ml $C_6H_6$. Reflux for 48 h. [b] Reaction monitored *via* g.l.c., quantitative conversion into three products. [c] According to g.l.c. analysis. Isolated yields after extraction and chromatography: (**2**) (23%), (**3**) (10%), (**4**) (35%). [d] Atom numbering: piperidine C-2, side chain C-1′. [e] Ligand priority sequence at C-1′ in compound (**1**) is reversed in compounds (**2**) and (**3**). [f] Absolute configuration determined by *X*-ray analysis (ref. 3). [g] Absolute configuration of HCl salt determined by *X*-ray analysis (ref. 3). [h] Yield not determined.

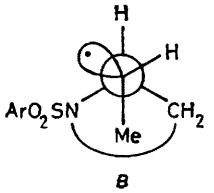
Therefore the two pairs of diastereomers of (**1**) were prepared, characterized, and subsequently their reactions were studied. The results are summarized in the Table.

Thus, the (2*R*),(1′*S*)-diastereomer of (**1**) gives (**2**) and (**3**) with complete inversion at C-1′, whilst the (2*R*),(1′*R*)-diastereomer gives these products with complete retention at C-1′.

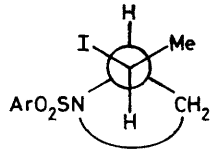
This behaviour can be rationalized in the following manner. Product formation from the intermediate (**5**) may take place from either conformation *A*,† arising from I-abstraction of the 2(*R*),(1′*R*)-iodide (**1**) or *B*, resulting from the 2(*R*),(1′*S*)-iodide and depending on the configuration of the starting iodide. For the 2(*R*),(1′*S*)-iodide the low-energy conformation in the solid state is represented by *C*, which has been established unequivocally by *X*-ray analysis.‡ $^1$H n.m.r. spectral data ($CDCl_3$ and $C_6D_6$) for the latter iodide also tend to confirm this conformational preference, which showed the Me and I substituents pointing away from the piperidine ring and the C-1 sidechain occupying an axial position.



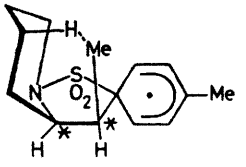

*A*




*B*




*C*

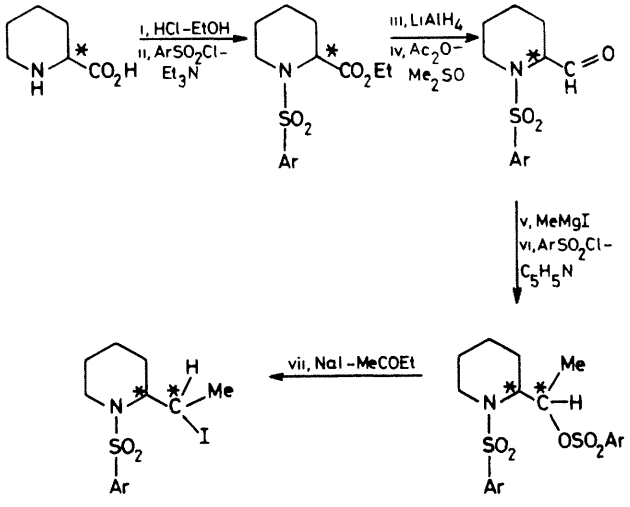



(**6**)

Upon ring closure of *B* in either a 1,5- or 1,6-mode a marked steric interaction of the 1,3-diaxial type is present in the transition state as indicated in (**6**) for the 1,5-process. Therefore a cyclisation *via B* is considered unfavourable. On the contrary, ring closure from *A* may proceed relatively easily and might therefore occur preferentially.

Interconversion of *B* to *A* requires rotation about the C-2–C-1′ bond and (possibly) radical inversion at C-1′. Because of the low energy of these processes the observed complete asymmetric induction in the formation of the (2*R*),(1′*S*) enantiomers of (**2**) and (**3**) can be adequately accounted for. Thus, regardless of the configuration of the diastereomeric precursors the conformation *A* is favoured at the radical centre in the transition states of the 1,5- and 1,6-addition processes.

The iodide diastereomers (**1**) were prepared according to the reaction sequence shown.




(**1**)

Enantiomer separation of (*R*,*S*)-pipecolinic acid has been carried out *via* crystallization with (*R*,*R*)-tartaric acid;[2] diastereomeric separation of the iodide (**1**) was effected *via* t.l.c. Optical purity of the materials was checked by g.l.c. and spectral analysis, and also by an independent synthesis of the (*S*)-pipecoline ethyl ester.[3]

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† For reasons of simplicity only pyramidal forms are represented. No assessment of the true radical shape is implied.

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[1] J. J. Köhler and W. N. Speckamp, *Tetrahedron Letters*, 1977, 631; *ibid.*, 1977, 635; *J.C.S. Chem. Comm.*, 1978, 166; J. J. Köhler, Ph.D. Thesis, University of Amsterdam, 1979.
[2] F. Mende, *Ber.*, 1896, **29**, 2887.
[3] T. Fuji and M. Miyashi, *Bull. Chem. Soc. Japan*, 1975, **48**, 1341.